PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
H270530 0004 WO PH		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/009337	20.08.2004	22.08.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/155, A61K31/366, A61K31/404, A61K31/40, A61K31/506, A61P3/06, A61P3/10, A61P9/00

Applicant
FOURNIER LABORATORIES IRELAND LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.06.2005	09.02.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/009337

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-20 as originally filed

   Claims, Numbers

   1-13 filed with the demand

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Item V:

1. The subject-matter of claims 1 to 12 relates to the use of metformin and a statin to control or decrease glycaemia in non insulin dependent diabetes subjects.
The subject-matter of claim 13 relates to a process to manufacture a kit comprising metformin and a statin for co-administration of both compounds.

2. None of the available prior art discloses either of the above subject-matter. The requirements of A. 33(2) are met.

3.1. D1 discloses that the concomitant use of pravastatin and metformin on patients suffering from a syndrome involving all of NIDDM, hypertension, dislipemia and obesity improves their lipids profile and atherogenic index.
D1 however is silent as to the effect on glucose blood level (glycaemia).
The present application shows that the combination statin+metformin reduces the glucose blood level more than metformin alone.
As this could not be inferred from D1, the subject-matter of claims 1 to 12 meets the requirements for inventive step (A. 33(3)).

3.2. This conclusion however does not apply to the subject-matter of claim 13 which concerns a kit (and not a specific therapeutic use). Even if according to D1 the statin and metformin are administered separately, the solution consisting in administering them together as a kit is a mere obvious alternative for which no inventive step can be acknowledged (A. 33(3)).

4. Contrary to the requirements of R. 5.1.a).ii) D1 is not cited in the description.

Amended claims for International Preliminary Examination

1. Use of metformin, a statin and one or more pharmaceutically acceptable excipients, for the manufacture of a pharmaceutical composition for controlling or decreasing glycaemia in non insulin dependent diabetes subjects.

2. The use according to claim 1, wherein the statin is selected from the group consisting of lovastatin, fluvastatin, atorvastatin, simvastatin, pravastatin, itavastatin and rosuvastatin.

3. The use according to claim 1 or 2, wherein metformin is in the form of a salt selected from the group consisting of the hydrochloride, acetate, benzoate, citrate, fumarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutamate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate.

4. The use according to any of claims 1 to 3, wherein metformin is in the form of a salt selected from the group consisting of the hydrochloride, fumarate, embonate, and chlorophenoxyacetate.

5. The use according to any of claims 1 to 4, wherein the statin is in the form of a salt selected from the group consisting of the sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion.

6. The use according to any of claims 1 to 5, wherein said composition contains from 0.1 to 100 mg of a statin.

7. The use according to any of claims 1 to 6, wherein said composition contains from 200 to 2000 mg of metformin.

8. The use according to any of claims 1 to 7, wherein the weight ratio of statin to metformin is in the range of about 1:2 to about 1:20000.

9. The use according to any of claims 1 to 8, wherein said composition is in the form of powders, tablets, coated tablets, dragees, troches, lozenges, dispersible granules, capsules or sachets.

10. The use according to any of claims 1 to 8, wherein said composition is in the form of a solution, a suspension or an emulsion.

11. The use according to any of claims 1 to 10, wherein the pharmaceutical composition is a controlled-release composition.

12. The use according to any of claims 1 to 11, wherein the pharmaceutical composition is administered orally.

13. Use of metformin and a statin in the manufacture of a kit comprising metformin, or one of its pharmaceutically acceptable salts, and a statin, or one of its pharmaceutically acceptable salts, for the simultaneous co-administration of metformin and the statin.